REMARKS

1. Applicants hereby submit the following:

[ ] a paper copy of a "Sequence Listing", complying with §1.821(c), to be incorporated into the specification as directed above;

[XX] an amendment to the paper copy of the "Sequence Listing" submitted on November 6, 2001, the amendment being in the form of substitute sheets;

[XX] the Sequence Listing in computer readable form, complying with §1.821(e) and §1.824, including, if an amendment to the paper copy is submitted, all previously submitted data with the amendment incorporated therein;

[ ] pursuant to §1.821(e), reference is made to the computer readable form filed on , in USSN , which presents the identical Sequence information, the use of which is now requested, in lieu of submitting a new computer readable form; and/or

[ ] a substitute computer readable form to replace one found to be damaged or unreadable.

[XX] 2. The description has been amended to comply with §1.821(d).

3. The undersigned attorney or agent hereby states as follows:

(a) this submission is not believed to include new matter [§1.821(g)];

(b) the contents of the paper copy (as amended, if applicable) and the computer readable form of the Sequence Listing, are believed to be the same [§1.821(f) and §1.825(b)];

(c) if the paper copy has been amended, the amendment is believed to be supported by the specification and is not believed to include new matter [§1.825(a)]; and

(d) if the computer readable form submitted herewith is a substitute for a form found upon receipt by the PTO to be damaged or unreadable, that the substitute data is believed to be identical to that originally filed [§1.825(d)].

4. Under U.S. rules, each sequence must be classified in <213> as an "Artificial Sequence", a sequence of

"Unknown" origin, or a sequence originating in a particular organism, identified by its scientific name.

Neither the rules nor the MPEP clarify the nature of the relationship which must exist between a listed sequence and an organism for that organism to be identified as the origin of the sequence under <213>.

Hence, counsel may choose to identify a listed sequence as associated with a particular organism even though that sequence does not occur in nature by itself in that organism (it may be, e.g., an epitopic fragment of a naturally occurring protein, or a cDNA of a naturally occurring mRNA, or even a substitution mutant of a naturally occurring sequence). Hence, the identification of an organism in <213> should not be construed as an admission that the sequence *per se* occurs in nature in said organism.

Similarly, designation of a sequence as "artificial" should not be construed as a representation that the sequence has no association with any organism. For example, a primer or probe may be designated as "artificial" even though it is necessarily complementary to some target sequence, which may occur in nature. Or an "artificial" sequence may be a substitution mutant of a natural sequence, or a chimera of two or more natural sequences, or a cDNA (i.e., intron-free

sequence) corresponding to an intron-containing gene, or otherwise a fragment of a natural sequence.

The Examiner should be able to judge the relationship of the enumerated sequences to natural sequences by giving full consideration to the specification, the art cited therein, any further art cited in an IDS, and the results of his or her sequence search against a database containing known natural sequences.

Attached hereto is a marked-up version of the changes made to the specification by the current amendment. The attached page is captioned "Version with markings to show changes made".

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the specification:

The paragraph beginning at line 21 of page 1 has been amended as follows:

Chymosin (EC 3.4.23.4) and pepsin (EC 3.4.23.1), the milk clotting enzymes of the mammalian stomach, are aspartic proteases belonging to a broad class of peptidases (Kappeler, 1998). Aspartic proteases are found in eukaryotes, retroviruses and some plant viruses. Eukaryotic aspartic proteases are monomers of about 35 kDa, which are folded into a pair of tandemly arranged domains with a high degree of similarity, i.e. 20% or higher. The overall secondary structure consists almost entirely of pleated sheets and is low in α-helices. Each domain contains an active site centred on a catalytic aspartyl residue with a consensus sequence [hydrophobic]-Asp-Thr-Gly-[Ser/Thr] (SEQ ID NO:7) which aids in maintaining the correct Φ-loop conformation of the site, and with multiple hydrophobic residues near the aspartic residue. The two catalytic sites are arranged face-to-face in the tertiary structure of correctly folded proteins. In bovine chymosin, the distance between the aspartic side chains is about 3.5 Å. The residues are reported to be extensively hydrogen bonded, concomitantly with the adjacent threonine residues, to the corresponding residues of the other domain or

the neighbouring atoms of the own domain, to stabilise the correct position. Optimum activity of an aspartic protease is achieved when one of the aspartic residues is protonated and the other one is negatively charged. The active sites of chymosin and other aspartic proteases are embedded, with low accessibility, in the middle of a cleft, about 40 Å in length, which separates the two domains, and which is covered by a flap that, in bovine and camel chymosin, extends from about Leu73 to Ile85 in the N-terminal domain.